



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 209/34, 403/06, 409/06, A61K 31/40, 31/415	A3	(11) International Publication Number: WO 99/48868 (43) International Publication Date: 30 September 1999 (30.09.99)
---	-----------	--

(21) International Application Number: PCT/US99/06468

(22) International Filing Date: 26 March 1999 (26.03.99)

(30) Priority Data:

60/079,713	26 March 1998 (26.03.98)	US
60/080,422	2 April 1998 (02.04.98)	US
60/081,792	15 April 1998 (15.04.98)	US
60/082,056	16 April 1998 (16.04.98)	US
60/089,397	15 June 1998 (15.06.98)	US
60/089,521	16 June 1998 (16.06.98)	US
60/098,783	1 September 1998 (01.09.98)	US

(71) Applicants (for all designated States except US): SUGEN, INC. [US/US]; 230 East Grand Avenue, South San Francisco, CA 94080 (US). NEW YORK UNIVERSITY [US/US]; 550 First Avenue, New York, NY 10016 (US). MAX-PLANCK INSTITUT FÜR BIOCHEMIE [DE/DE]; Am Klopferspitz 18A, D-82152 Martinsried (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): FONG, Annie [US/US]; 811 Shetland Place, Sunnyvale, CA 94087 (US). HAN-NAH, Alison [US/US]; 3449 Brittan Avenue, San Carlos, CA 94070 (US). HARRIS, David, G. [US/US]; 417 Roosevelt Way, San Francisco, CA 94114 (US). HIRTH, Peter [DE/US]; 334 Collingwood Street, San Francisco, CA 94114 (US). HUBBARD, Steven, R. [US/US]; 5465 Sylvan Avenue, Riverdale, NY 10471 (US). LANGECKER, Peter [US/US]; 17610 Via Sereno, Monte Sereno, CA 95030 (US). LIANG, Congxin [CN/US]; 726 W. Remington Drive, Sunnyvale, CA 94087 (US). MCMAHON, Gerald [US/US]; 1800 Schultz Road, Kenwood, CA 95452 (US). MOHAMMADI, Moosa [IR/US]; 564 First Avenue #12F, New York, NY 10016 (US). SCHLESSINGER, Joseph [IL/US]; 37

Washington Square West, New York, NY 10011 (US). SHAWVER, Laura, K. [US/US]; 216 Cotter Street, San Francisco, CA 94112 (US). SUN, Li [CN/US]; 64 Rock-harbor Lane, Foster City, CA 94404 (US). TANG, Peng, C. [US/US]; 827 Camino Ricardo, Moraga, CA 94556 (US). ULLRICH, Axel [DE/DE]; Turkenstrasse 104, D-80799 München (DE).

(74) Agents: WARBURG, Richard, J. et al.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071-2066 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

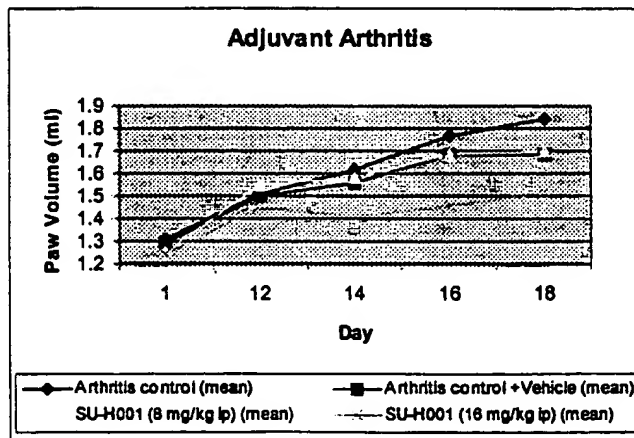
(88) Date of publication of the international search report:

24 February 2000 (24.02.00)

(54) Title: HETEROCYCLIC CLASSES OF COMPOUNDS FOR THE MODULATING TYROSINE PROTEIN KINASE

(57) Abstract

The invention relates to certain indolinone-based and pyrazolylamide-based compounds, their method of synthesis, and combinatorial libraries consisting of the compounds. The invention also relates to methods of modulating the function of protein kinases using these compounds and methods of treating diseases by modulating the function of protein kinases and related signal transduction pathways.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/06468

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D209/34 C07D403/06 C07D409/06 A61K31/40 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 50356 A (SUGEN INC) 12 November 1998 (1998-11-12)	1-7,62
X	* overlap of chemical formula, see claim 1, definition of Q = 3,5 * the whole document ---	39-61
X	WO 98 07695 A (HIRTH KLAUS PETER ;SHAWVER LAURA KAY (US); SUGEN INC (US); TANG PE) 26 February 1998 (1998-02-26)	1-7,62
Y	* overlap of chemical formula, see e.g. claim 6, definition of R8 and R9, claim 10, definition of R5 and R6 etc. * the whole document ---	39-61
Y	WO 94 14808 A (ERBA CARLO SPA) 7 July 1994 (1994-07-07) cited in the application the whole document ---	1-7,62
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

16 November 1999

Date of mailing of the international search report

10. 12. 99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stellmach, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/06468

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SPADA A P ET AL: "SMALL MOLECULE INHIBITORS OF TYROSINE KINASE ACTIVITY" EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 5, no. 8, 1 January 1995 (1995-01-01), pages 805-817, XP000567587 ISSN: 1354-3776	1-7,62
Y	* see page 812, Fig.2, page 813, Tab.1 * the whole document	8-19
Y	WO 96 00226 A (PHARMACIA SPA ;BUZZETTI FRANCO (IT); BRASCA GABRIELLA MARIA (IT);) 4 January 1996 (1996-01-04)	1-7,62
X	the whole document	39-50
Y	WO 96 16964 A (PHARMACIA SPA ;BUZZETTI FRANCO (IT); BRASCA GABRIELLA MARIA (IT);) 6 June 1996 (1996-06-06)	1-7,62
Y	the whole document	39-50
Y	WO 91 13055 A (ERBA CARLO SPA) 5 September 1991 (1991-09-05)	1-7,62
Y	the whole document	
Y	WO 92 07830 A (PFIZER) 14 May 1992 (1992-05-14)	1-7,62
X	the whole document	39-50
Y	TRAXLER,P.M.: "Protein tyrosine kinase inhibitors in cancer treatment" EXP.OPIN.THER.PATENTS, vol. 7, no. 6, 1997, pages 571-588, XP002122590 LONDON * see p.584, par. 8.2 * the whole document	1-19, 39-62
X	WO 92 20642 A (RHONE POULENC RORER INT) 26 November 1992 (1992-11-26) * overlapping chemical formula * the whole document	8-19,62
Y	WO 95 24190 A (YISSUM RES DEV CO ;SUGEN INC (US)) 14 September 1995 (1995-09-14) " see fig 3e, p.3/12, ex. M17, M18 * the whole document	8-19,62

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/06468

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>LEVITZKI A ET AL: "TYROSINE KINASE INHIBITION: AN APPROACH TO DRUG DEVELOPMENT" SCIENCE,US,AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, vol. 267, March 1995 (1995-03), page 1782-1788 XP002048355 ISSN: 0036-8075 * see p.1784/1785, ex.AG1112 * the whole document</p>	8-19,62
Y	<p>GAZIT,A. ET AL.: "Tyrphostins. 2. Heterocyclic and alpha-Substituted Benzylidenmalonitrile Tyrphostins as Potent Inhibitors of EGRF Receptor and ErbB2/neu Tyrosine Kinases" J.MED.CHEM., vol. 34, no. 6, June 1991 (1991-06), pages 1896-1907, XP000472938 WASHINGTON * see p.1897, table 1, ex. 11 * the whole document</p>	8-19,62
Y,P	<p>SUN,LO. ET AL.: "Synthesis and Biological Evaluation of 3-Substituted Indolin-2-ones : A novel Class of Tyrosine Kinase Inhibitors That Exhibit Selectivity toward Particular Receptor Tyrosine Kinases" J.MED.CHEM., vol. 41, no. 14, 2 July 1998 (1998-07-02), pages 2588-2603, XP002122185 WASHINGTON</p>	8-19,62
X,P	<p>* see p.2589, chart 1, p.2591, scheme 4,p.2596, table 5 * the whole document</p>	39-50
X,P	<p>WO 98 56376 A (SUGEN INC) 17 December 1998 (1998-12-17) the whole document</p>	8-19,62
X	<p>WO 96 40116 A (SUGEN INC) 19 December 1996 (1996-12-19)</p>	39-50,62
Y	<p>* overlap of chemical formula, see claims 7,8,14,20, the definition of the substituent A * the whole document</p>	51-61

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/06468

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>MOHAMMADI M ET AL: "STRUCTURES OF THE TYROSINE KINASE DOMAIN OF FIBROBLAST GROWTH FACTOR RECEPTOR IN COMPLEX WITH INHIBITORS"</p> <p>SCIENCE,US,AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, vol. 276, no. 5314, page 955-960 XP002065235 ISSN: 0036-8075 * see p.956, SU5402 * the whole document</p> <p>---</p>	39-62
P,X	<p>WO 98 45708 A (CLARY DOUGLAS ;SUGEN INC (US)) 15 October 1998 (1998-10-15) * see p.55, indolines 1 - 6 * the whole document</p> <p>-----</p>	39-50

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/06468

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 63-104 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 20-38
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-19, 39-62
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.2

Claims Nos.: 20-38

Present claims 8 -19 and 62 relate to an extremely large number of possible compounds with only a small part being fixed (see in particular the definition of p together with K and L). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of example 2, pages 92-94, see also examples of tables 10 and 11 (pages 27-29 e.g . those compounds prepared in these examples and closely related analogues/homologues compounds).

Present claims 1-7 and 62 relate to an extremely large number of possible compounds, with partially completely different chemical character, see claim 6). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of example 1 (pages 90-92 e.g those compounds etc. prepared in these examples and closely related homologous compounds etc.).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7,62

Tricyclic 3-methylene-2-oxindole based compounds of formula I and II

2. Claims: 8-19,62

Pyrazole-amide based compounds

3. Claims: 20-38,62

3-Tricyclic substituted 3-methylene-2-oxindole based compounds and intermediates for their production

4. Claims: 39-50,62

3-Monocyclic substituted 3-methylene-2-oxindole based compounds

5. Claims: 51-61,62

6-Phenyl-3-methylene-2-oxindole based compounds

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/06468

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9850356 A	12-11-1998	AU 7684298 A AU 7661498 A	27-11-1998 27-11-1998
WO 9807695 A	26-02-1998	AU 4155697 A EP 0929520 A	06-03-1998 21-07-1999
WO 9414808 A	07-07-1994	AT 181074 T AU 670488 B AU 5810594 A CA 2126228 A CN 1093707 A DE 69325262 D EP 0626963 A FI 943838 A HU 67431 A IL 108087 A JP 7504208 T MX 9400206 A NZ 259330 A PL 304894 A US 5397787 A ZA 9309578 A	15-06-1999 18-07-1996 19-07-1994 07-07-1994 19-10-1994 15-07-1999 07-12-1994 19-08-1994 28-04-1995 30-09-1997 11-05-1995 29-07-1994 21-12-1995 09-01-1995 14-03-1995 11-08-1994
WO 9600226 A	04-01-1996	AU 2671695 A CA 2168659 A CN 1129941 A EP 0715628 A FI 960751 A HU 74609 A JP 9502457 T NO 960713 A PL 313166 A US 5663346 A ZA 9505223 A	19-01-1996 04-01-1996 28-08-1996 12-06-1996 19-02-1996 28-01-1997 11-03-1997 22-02-1996 10-06-1996 02-09-1997 31-01-1996
WO 9616964 A	06-06-1996	AU 3926295 A CA 2180730 A CN 1139929 A EP 0741726 A FI 962954 A HU 74875 A JP 9508924 T NO 963066 A NZ 295668 A PL 315689 A US 5719135 A ZA 9509927 A	19-06-1996 06-06-1996 08-01-1997 13-11-1996 24-07-1996 28-02-1997 09-09-1997 23-07-1996 24-11-1997 25-11-1996 17-02-1998 10-06-1996
WO 9113055 A	05-09-1991	AT 131470 T AT 184000 T AU 652740 B AU 7241291 A CA 2053253 A DE 69115379 D DE 69115379 T DE 69131581 D DK 470221 T EP 0470221 A	15-12-1995 15-09-1999 08-09-1994 18-09-1991 29-08-1991 25-01-1996 15-05-1996 07-10-1999 29-01-1996 12-02-1992

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/06468

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9113055 A		EP 0662473 A	12-07-1995
		ES 2083569 T	16-04-1996
		GR 3018891 T	31-05-1996
		HU 210791 B	28-07-1995
		IE 73666 B	02-07-1997
		IL 97049 A	31-10-1995
		JP 4506081 T	22-10-1992
		NZ 237182 A	23-12-1993
		PT 96897 A,B	31-10-1991
		RU 2091369 C	27-09-1997
		US 5374652 A	20-12-1994
		US 5488057 A	30-01-1996
		US 5627207 A	06-05-1997
WO 9207830 A	14-05-1992	PT 99350 A	30-10-1992
WO 9220642 A	26-11-1992	AT 159009 T	15-10-1997
		AU 658646 B	27-04-1995
		AU 1993492 A	30-12-1992
		CA 2102780 A	11-11-1992
		DE 69222637 D	13-11-1997
		DE 69222637 T	26-02-1998
		DK 584222 T	23-02-1998
		EP 0584222 A	02-03-1994
		ES 2108120 T	16-12-1997
		GR 3024955 T	30-01-1998
		JP 6507643 T	01-09-1994
		MX 9202181 A	01-05-1993
		SG 64322 A	27-04-1999
		US 5409930 A	25-04-1995
		US 5480883 A	02-01-1996
		US 5710158 A	20-01-1998
		US 5795889 A	18-08-1998
		US 5646153 A	08-07-1997
		US 5721237 A	24-02-1998
		US 5714493 A	03-02-1998
		US RE36256 E	20-07-1999
WO 9524190 A	14-09-1995	AU 2096895 A	25-09-1995
		US 5789427 A	04-08-1998
		US 5773476 A	30-06-1998
WO 9856376 A	17-12-1998	AU 8071698 A	30-12-1998
WO 9640116 A	19-12-1996	US 5880141 A	09-03-1999
		AU 706597 B	17-06-1999
		AU 6044196 A	30-12-1996
		BR 9606410 A	30-12-1997
		CA 2192797 A	19-12-1996
		DE 29623744 U	30-09-1999
		EP 0769947 A	02-05-1997
		EP 0934931 A	11-08-1999
		HU 9701694 A	28-06-1999
		JP 10504323 T	28-04-1998
		NO 965377 A	12-02-1997
		NZ 310109 A	28-01-1999
		US 5792783 A	11-08-1998
		US 5883116 A	16-03-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/06468

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9640116 A		US 5834504 A	10-11-1998
		US 5886020 A	23-03-1999
		US 5883113 A	16-03-1999
WO 9845708 A	15-10-1998	AU 6887698 A	30-10-1998